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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,957	02/09/2001	Kristi D. Snell	MBX 038	7578

23579 7590 10/23/2002

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EXAMINER
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BAUM, STUART F

ART UNIT	PAPER NUMBER
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1638

DATE MAILED: 10/23/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/779,957

Applicant(s)

SNELL, KRISTI D.

Examiner

Stuart F. Baum

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 August 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-28 is/are pending in the application.
- 4a) Of the above claim(s) 3-5, 17 and 19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 6-16, 18 and 20-28 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. Applicant's election with traverse of Group II, claims 1, 2, 6-16, 18, and 20-28 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the restriction is improper for dividing up claims directed to 1) bacterial and yeast cells; 2) plant cells; and 3) mammalian cells using linking claim language but rather an election of species is necessary. This is not found persuasive because the linking claims are generic that do not list species. Furthermore, they are distinct cells, one from the other, that are restrictable and are not species.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-28 are pending.

Claims 3-5, 17, and 19 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-2, 6-16, 18, and 20-28 will be examined on their merits.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 11, 12, 16, 25 and 26 and all subsequent dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 25 are indefinite and unclear in the recitation "wherein one or more inteins comprise exteins". It is not clear how an extein can be part of an intein.

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Claims 12 and 26 have a “)” one line 2, after the word dehydrogenases, which needs to be removed.

In Claim 16, eukaryotic is misspelled.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, 4, 6-16, 18, and 20-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Applicant claims a method for expressing multiple genes in a cell and a DNA construct for expression of multiple gene products in a cell, both of which comprising a promoter, multiple genes encoding one or more proteins, a first intein sequence fused to the portion of the gene encoding the carboxy-terminus of a first encoded protein, a second intein sequence fused to the portion of the gene encoding the carboxy-terminus of a second encoded protein and a transcription termination sequence, wherein the promoter is operable in plant cells, and the proteins are either the same or are different enzymes.

The Applicant describes a system in which multiple genes can be transcribed and translated using one promoter and one 3' termination sequence, with intein fragments separating the desired proteins. The theoretical system is designed using the components of the protein splicing process associated with intein excision/extein ligation that has been studied by previous

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researchers (cited references, page 7, lines 11-21). The Applicant does not identify structural features unique to the protein splicing process which are described as a construct comprising intein and extein sequences, the functional domains of the protein splicing process nor the overall function of the protein splicing process. The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Given the lack of description for the intein/extein protein splicing process, it remains unclear what features identify an intein that can be used to separate contiguously arranged amino acids that encode more than one functional protein after the excision of one or more intein sequences. Since an intein that can be used to separate proteins has not been described by specific structural features or by specific function, the specification fails to provide an adequate written description to support the generic claims.

5. Claims 1-2, 4, 6-16, 18, and 20-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Applicant claims a method for expressing multiple genes in a cell and a DNA construct both of which comprising a promoter, multiple genes encoding one or more proteins, a first intein sequence fused to the portion of the gene encoding the carboxy-terminus of a first encoded protein, a second intein sequence fused to the portion of the gene encoding the carboxy-terminus of a second encoded protein and a transcription termination sequence, wherein the promoter is operable in plant cells, and the proteins are either the same or are different enzymes.

The Applicant describes a system in which multiple genes can be transcribed and translated using one promoter and one 3' termination sequence, with intein fragments separating the desired proteins. The system is designed using in theory, the components of the protein splicing process that has been studied by previous researchers (cited references, page 7, lines 11-21). The Applicant only prophetically describes the invention in the Example section of the specification (pages 18-21) with most of the explanation dealing with the production of isolated protoplasts. Applicant does not reduce to practice the invention so that one skilled in the art can make and/or use the invention commensurate with the scope of the claims.

Producing proteins using a posttranslational editing process that removes an intein from in between separate proteins can produce unpredictable results. The Applicant does not teach how long the intein segments should be or what the intein sequence should be. Applicant only specifies that the 3'-terminal extein (the protein bordering the intein sequence) is engineered to contain a glycine or alanine residue. Perler (1998, Cell 92:1-4) teaches that there are ten conserved intein motifs, none of which are included in Applicant's claimed invention. Evans et al (2000, The Journal of Biological Chemistry 275 (13): 9091-9094) teach that the number of C-terminal extein amino acid residues has an effect on protein splicing as does the temperature at

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which the organism is grown (page 9093, right column, 1<sup>st</sup> and 2<sup>nd</sup> paragraphs and 4<sup>th</sup> and 3<sup>rd</sup> lines from the bottom of the column) Morassutti et al (2002, FEBS 519:141-146) teach that a nucleophilic agent (e.g. 1,4-dithiothreitol) was used to initiate the self-catalytic cleavage of the intein-chitin binding domain from the extein during protein purification procedures (page 144, right column, 1<sup>st</sup> paragraph) which Applicant does not address in their invention. Perler teaches that “the *Chlamydomonas eugametos* ClpP intein failed to splice in *E. coli* unless the intein penultimate Gly was mutated to His” (page 1, right column, end of 2<sup>nd</sup> paragraph). Perler continues by stating that not all inteins work in *E. coli*, “possibly due to misfolding, inhibiting intracellular pH, redox potential, etc” (*supra*) all of which are variables encountered in all living organisms. Perler states that “protein splicing is less efficient when an intein is expressed within a foreign protein”, because “proximal foreign extein residues can potentially disturb the intein active-site by steric hindrance” (page 1, 3<sup>rd</sup> paragraph). Perler concludes by stating “future experiments are also needed to define suitable locations for intein insertion if inteins are to be useful in protein engineering” (*supra*).

Given the unpredictability of using the claimed invention for the reasons stated above; and given the lack of examples and guidance in using any intein sequence to separate and facilitate protein processing of a linear array of one or multiple translated proteins; and given the state of the art that teaches that there are many variables whose conditions need to be empirically established before an intein can be used in a heterologous system, it would require undue experimentation by one skilled in the art to make and/or use the broadly claimed invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Chong et al (The Journal of Biological Chemistry 271:22159-22168, list in IDS)

The Applicant claims a method for expressing multiple genes in a cell and a DNA construct both of which comprise a promoter, multiple genes encoding one or more proteins, a first intein sequence fused to the portion of the gene encoding the carboxy-terminus of a first encoded protein, a second intein sequence fused to the portion of the gene encoding the carboxy-terminus of a second encoded protein and a transcription termination sequence.

Chong et al teach a construct designed to express proteins in *E. coli* in which the construct comprises a first gene fused to an intein and a second gene fuse to an intein all of which are operably linked to a promoter sequence operable in *E. coli* and a transcription termination sequence ( see Material and methods section, page 22160 through 22162) and as such, Chong et al anticipate the claimed invention.

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart Baum whose telephone number is (703) 305-6997. The examiner can normally be reached on Monday-Friday 8:30AM – 5:00PM.



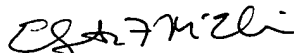
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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 or (703) 305-3014 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the legal analyst, Sonya Williams, whose telephone number is (703) 305-2272.

Stuart Baum Ph.D.

October 19, 2002

  
ELIZABETH F. McELWAIN  
PRIMARY EXAMINER  
GROUP 1800